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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/312,351	05/14/1999	JON A. WOLFF	MIRUS.006	2480

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/15/2003 22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/312,351	Applicant(s) Wolff et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 25, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-11, 15-17, and 24-28 is/are pending in the application.

4a) Of the above, claim(s) 1-6 and 15-17 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 7-11 and 24-28 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2002, paper number 27, has been entered.

DETAILED ACTION

This application filed May 14, 1999, claims benefit to provisional application 60/085,764, filed May 16, 1998.

As indicted in the request for continued examination Applicants' after final amendment filed October 4, 2002, paper number 19, has been entered. Claims 19-23 have been canceled. Claims 7 and 24 have been amended.

Claims 1-11, 15-17, 24-28 are pending. Claims 1-6, 15-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 5. Claims 7-11 and 24-28 are currently under examination.

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Specifically, at page 54, line 18, an eight amino acid sequence is present, but it is not identified with a SEQ ID NO. Applicant's attention is directed to the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

In the instant case, there is no sentence providing a specific claim for priority, only a listing of a related application. If applicant desires priority under 35 U.S.C. 119(e) based upon a

previously filed copending application, specific reference to the earlier filed application must be made in a sentence in the first line of the instant application.

Please note, if the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions,Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

on the first page of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-11, 24-28 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Applicants note that at page 19, lines 12-17 of the present specification supports the term "physiological condition". See Applicants' amendment, top of page 4.

Upon review of the indicated portion of the specification, Examiner agrees that literal support for physiological conditions is provided by the present specification where the meaning of the phrase a "disulfide bond that is labile under physiological conditions" is set forth. Therefore, the new matter rejection is withdrawn.

Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-11 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth below and in the previous office action, paper number 18.

Applicants argue that the term physiological condition is defined by the specification, pointing to page 19, lines 12-17. See Applicants' amendment, top of page 4. Applicants' arguments have been fully considered but not found persuasive.

It is noted that at page 19, lines 12-15, that the phrase "A disulfide bond that is labile under physiological conditions" is defined, however not the metes and bounds of the 'physiological conditions' at which the lability is measured. Applicants arguments are unpersuasive because as noted in the previous office action "physiological condition" is not specifically defined in the present specification, and it is unclear what the metes and bounds of this term encompasses. The metes and bounds of this term would vary depending on the context, for example between *in vivo* and *in vitro*, or even a physiological condition as defined for a particular organism in its own unique environment (for example bacteria, yeast or archeobacteria). The metes and bounds of the claims are indefinite because a compound which is labile at one condition which could be considered physiological may not be labile at a second condition which is also considered physiological. Additionally, it is noted that claim 7 recites the limitation "and is cleaved more rapidly than oxidized glutathione" to further define the disulfide bond, however it is also used by the specification define the phrase "disulfide bond that is labile under physiological conditions". In this case, it appears that this specific limitation is set forth to

further limit the properties of the disulfide bond, otherwise this limitation is redundant in light of a "disulfide bond that is labile under physiological conditions" as set forth in the specification. Notwithstanding, with or with the limitation of cleavage which is more rapid than oxidized glutathione, the metes and bounds of the term are indefinite because a single compound may or may not meet the limitation of the claims depending on the context at which is analyzed. Since the specific context of physiological condition is not defined, the artisan can not specifically define the metes and bounds of the claims, and therefore the claim is indefinite.

Claims 7-11 and 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 7 is confusing in the recitation of "a sulfide bond, wherein at least two reactable groups, at least one on each side of the disulfide bond, have reacted to form a covalent bond" because it is unclear if the claim is directed to the disulfide containing compound which has two reactable groups, or if it is directed to the disulfide containing compound which looses the reactable groups, or if the reactable groups are present once a covalent bond would be made with said groups. As set forth in the preamble, the claim is directed to a composition, and while limitations indicate functional limitations suggesting that the claim is directed to a product by process, such "have reacted", because no specific method steps are set forth the claim is unclear what are the functional limitations specifically encompassed by the the disulfide containing compound in the composition. The claim is unclear

to what specific molecules are contemplated, what is their relationship to the labile disulfide bond, and how they should be or are covalently attached on either side of the disulfide bond. It is noted that 'reactable groups' is not specifically defined in the specification, but the specification describes a possible labile disulfide bond containing bifunctional molecules and that the molecules have 'reactive ends' for crosslinking and chemical attachment of other molecules (page 19, lines 19-30). However, while the specification disucsses the addition of other biological active compounds to bifunctional crosslinkers, it also discusses the properties and synthesis of labile disulfide containing molecules contemplated (pages 1-18). Since any atom molecule can be reacted with another atom molecule, in particular in the synthesis of the general disulfide bond containing compounds it is unclear if even a disulfide bond with a carbon on either side is encompassed by the claim because these were reactable groups which were covalently attached to the sulfide atoms to form a compound. Claim 7 is vague and unclear in the recitation of "have reacted with one or more molecules" because it is unclear if each of the reactive groups must be reacted with one or more molecules or if a single reactive group could be modified with a one molecule to meet the limitation of the claim. The metes and bound of the claims are indefinite because the specific properties of the reactive groups and/or modification of these groups is not clearly set forth in the claim. More clearly describing or defining the nature of the disulfide containing compound with respect to each of the components present in the compound would obviate the basis of the rejection.

Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 8 and 9 recite the limitation "the compound", however there is insufficient antecedent basis for this limitation in the claim. Neither independent claim 7 nor claims 8 and 9 provide a literal basis for a compound. Claim 7 encompasses a composition, and while the composition could be interpreted to comprise multiple compounds, it is unclear to which possible or specific compound in claim 7 claims 8 and 9 refer.

Claims 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 24 is vague and indefinite in the recitation of 'such that the disulfide bond is cleaved more rapidly than oxidized glutathione' because the specific condtions at which this limitation is measured. The metes and bounds of the claims are indefinite because a compound which is labile at one condition may not be labile at a second condition. The metes and bounds of the term are indefinite because a single compound may or may not meet the limitation of the claims depending on the context at which is analyzed. Since the specific context of the condition is not defined, the artisan can not specifically define the metes and bounds of the claims, and therefore the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-11 stand rejected under 35 U.S.C. 102(b) as being anticipated by the cross-linkers taught by Pierce (page T-172, 1994), as evidence by Arpicco *et al.* (Bioconjug Chem, 1997) for the reasons set forth below and in the previous office action, paper number 18.

Applicants note the amendments to the claims to include two reactable groups on either side of the disulfide linkage, and argue that the present specification teaches that the reactable groups contemplated are not the disulfide bond. More specifically, Applicants' argue that the crosslinker taught by Pierce would use the pyridyl dithio to form a new disulfide bond, and depending on the structure of the free thiol may or may not be physiologically labile (Applicants' amendment, pages 4-5). Applicants' review the basis for the stability of a disulfide bond as it is related to the pKa of the respective thiol, noting that art does not teach a substituted pyridine thiol and that any substitution on the pyridine nitrogen would decrease the stability of a disulfide bond (page 5). A more detailed analysis of the pKa of cysteine derived compounds is provided, noting the effects of specific substitutions on the measured pKa and the predictability of the trends for a given substitution and its affect on a pKa for modificaitons lose to the thiol (pages 5-

6) and modifications which are more distant (pages 6-7). See Applicants' amendment, pages 4-8. Applicants' arguments have been fully considered but not found persuasive.

The amendments to the claims are noted, however as discussed in the basis of the rejection made under 35 USC 112, second paragraph, because the claim can be interpreted to encompass a labile disulfide bond comprising a reactable group on either side of the disulfide bond, the linker taught by Pierce anticipates the claims. Because the nature of the "one or more molecules" covalently linked is not clearly defined in relation to the sulfide bond, the pyridyl group itself will meet the limitation of the claim if the sulfide bond is more labile than glutathione since the ring and any molecule in the ring will meet the limitation of a molecule as set forth in the claim. As noted in the previous office action, the cross-linking compounds taught in Pierce are known to be labile *in vivo* as evidenced by Arpicco *et al.*

The claims encompass a product, and not a product by process, therefore any product that has a disulfide bond which is more labile that glutathione and two reactable groups anticipate the claims. Applicants arguments directed to the effect of the modification of the nitrogen on the pyridyl group on the disulfide bond are noted, however modification of this bond would not be required to meet the limitations encompassed by the claim if one interprets the claim to encompass a disulfide bond comprising two reactable groups on either side of said disulfide bond.

it is not clear if the claim encompasses a disulfide bond with two reactable groups or if it encompasses a disulfide bond in which the reactive groups have been modified

The claims have been amended to recite a composition comprising a disulfide bond that is labile under physiological conditions and cleaved more rapidly that oxidized glutathione. A review of the specification provides several formulas of compounds which teach compounds which would meet the limitation of the instantly claimed compound. For example, page 5, defines a formula for a disulphide compound and on page 7 of the specification teaches a more defined compound that contains aromatic rings. The cross-linking compounds taught in Pierce are known to be labile *in vivo* as evidenced by Arpicco *et al.* The limitations in the dependent claims such as polymer and ligand are not specifically defined in the present specification, and the $-(CH_2)_5-$ can serve as a polymer and the sulfosuccinimidyl group can be a non-specific ligand (see sulfo-LC-SMPT). Given the broad limitations of the claims, and specific nature of the composition as it is defined under physiological conditions, the disulphide cross linkers taught in Pierce meet the limitation set forth in the claims.

Claims 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Arpicco *et al.* (Bioconjug Chem, May, 1997).

Double Patenting

Claims 19-23 objected to under 37 CFR 1.75 as being a substantial duplicate of claims 7-11 is withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

Joseph T. Woitach

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